7. Rhinitis and sinusitis

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Rhinitis and sinusitis are prevalent medical conditions that are often associated with each other and may result in significant morbidity and medical costs. They can cause systemic symptoms, decrease quality of life, and result in reduced workplace productivity and missed school days. Appropriate management of rhinitis or sinusitis may be an important component in effective management of coexisting or complicating conditions, such as asthma, allergic conjunctivitis, or chronic otitis media. Rhinitis may be caused by allergic, non-allergic, infectious, hormonal, occupational, and other factors. Defining the basis for rhinitis in an individual is important in selection of therapeutic options. Rhinitis and sinusitis may be difficult to distinguish from each other on the basis of history alone. Although most acute upper respiratory infections are viral and do not require antibiotic treatment, persistence of symptoms for ≥7 days makes acute bacterial sinusitis more likely and antibiotics an appropriate consideration. Radiographic imaging is not required for diagnosis of acute, uncomplicated sinusitis, although CT scans are indicated in evaluation of suspected chronic sinusitis or treatment failures. Chronic sinusitis may have an infectious or non-infectious basis. Underlying disorders that predispose to chronic sinusitis should be identified and treated as part of the treatment of chronic sinusitis. (J Allergy Clin Immunol 2003;111:S520-9.)

Key words: Rhinitis, sinusitis, allergy, diagnosis, treatment, antihistamines, corticosteroids, antibiotics

Abbreviations used
ACE: Angiotensin converting enzyme
BID: Twice daily
CD: Cluster of differentiation
CT: Computerized tomography
FESS: Functional endoscopic sinus surgery
HPA: Hypothalamic-pituitary-adrenal axis
IgA: Immunoglobulin A
IgE: Immunoglobulin E
IL: Interleukin
LT: Leukotriene
MRI: Magnetic resonance imaging
NANC: Non-adrenergic, non-cholinergic system
NARES: Nonallergic rhinitis with eosinophila syndrome
NSAID: Non-steroidal anti-inflammatory drug
PGD: Prostaglandin
QD: Each day
TH: T-lymphocyte helper

Rhinitis and sinusitis are prevalent medical conditions that may cause significant morbidity and medical treatment costs. They can decrease quality of life, and result in reduced workplace productivity and missed school days.[1,2] Appropriate management of rhinitis or sinusitis may be an important component in effective management of coexisting or complicating conditions, such as asthma, allergic conjunctivitis, nasal polyposis, or chronic otitis media.[1-3]

RHINITIS

Background

Although "rhinitis" strictly means inflammation of the nasal mucous membranes, inflammatory cell infiltrates do not always characterize some disorders termed rhinitis. Rhinitis can be more practically viewed as a heterogeneous group of nasal disorders characterized by 1 or more of the following symptoms: sneezing, nasal itching, rhinorrhea, and nasal congestion. Rhinitis may be caused by allergic, non-allergic, infectious, hormonal, occupational, and other factors.[1,3] Allergic rhinitis is the most common type of chronic rhinitis, but 30%-50% of patients with rhinitis have non-allergic causes.[4]

PATHOGENESIS

Nasal anatomy and physiology

The nasal cavity is divided by the nasal septum, which is composed of cartilage more distally and bone more proximally. The inferior, middle, and superior turbinates in the nasal cavity promote air filtration, humidification, and temperature regulation. The nasal cavity and turbinates are lined with mucosa comprised of pseudostratified columnar ciliated epithelium that overlies a basement membrane and the submucosa (lamina propria). The submucosa consists of serous and seromucous nasal glands, nerves, extensive vasculature, and cellular elements. Overlying the nasal epithelium is a thin layer of mucus that dynamically moves via ciliary action to the posterior nasopharynx. Infections (viral or bacterial) and allergic inflammation impair mucociliary clearance.[5] Because of the highly vascular nature of nasal tissues, vascular changes can lead to significant nasal obstruction.[6]

Vasoconstriction and consequent decreases in nasal airway resistance result from sympathetic nerve stimulation. Parasympathetic nerve stimulation promotes secretion from nasal airway glands and nasal congestion. The nasal mucosa also contains nerves of the non-adrenergic, non-cholinergic system (NANC). Neuropeptides from the latter nerves (substance P, neurokinin A and K, and calci-

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tonin gene-related peptide) are suspected to play a role in vasodilatation, mucus secretion, plasma extravasation, neurogenic inflammation, and mast cell nerve interactions, but the magnitude of their role is uncertain.[3,7]

ALLERGIC RHINITIS

Pathophysiology

Common allergens causing allergic rhinitis include proteins and glycoproteins in airborne dust mite fecal particles, cockroach residues, animal danders, molds, and pollens. Upon inhalation, allergen particles are deposited in nasal mucus, with subsequent elution and diffusion into nasal tissues. In addition, allergic responses may be caused by small molecular weight chemicals in occupational agents or drugs that act as haptens that react with self proteins in the airway to form complete allergens.[3] In the nose, the sensitization process is initiated when antigen-presenting cells (dendritic cells, especially CD1+ Langerhans-like cells, and macrophages) present allergen to CD4+ T lymphocytes.[8] Stimulated $CD4^+$ TH2 cells release IL-3, IL-4, IL-5, IL-13 and other cytokines that lead to a cascade of events that promote local and systemic IgE production by plasma cells as well as chemotaxis, and inflammatory cell recruitment, localization, proliferation, activation, and prolonged survival within the airway mucosa.[3]

Early/immediate allergic response

Within minutes of inhalation of allergen in sensitized individuals, allergens are recognized by IgE fixed to mast cells and basophils, causing degranulation and release of preformed mediators such as histamine and tryptase, and the rapid de novo generation of mediators, including cysteinyl-leukotrienes (LTC_4, LTD_4, and LTE_4) and prostaglandin D_2 (PGD_2). Mediators cause plasma leakage from blood vessels and dilation of AV arteriole venule anastomoses with consequent edema, pooling of blood in the cavernous sinusoids (the overwhelming cause of the congestion of allergic rhinitis), and occlusion of nasal passages. Mediators also stimulate active secretion of mucus from glandular and goblet cells. Histamine elicits itching, rhinorrhea, and sneezing whereas other mediators such as leukotrienes and PGD_2 likely have more important roles in development of nasal congestion.[3,9] Stimulation of sensory nerves leads to perception of nasal itch and congestion, and systemic reflexes that cause sneezing paroxysms.[10]

Late-phase response

Mediators and cytokines released during the early phase set off a cascade of events over the ensuing 4-8 hours that lead to an inflammatory response called the late response. Although this reaction may be clinically similar to the immediate reaction, nasal congestion is more prominent.[9] Mediators and cytokines released during the early response act upon post-capillary endothelial cells to promote vascular cell adhesion molecule (VCAM) and E-selectin expression that promotes adherence of circulating leukocytes, such as eosinophils, to endothelial cells. Factors with chemoattractant properties, such as IL-5 for eosinophils, promote the infiltration of the superficial lamina propria of the mucosa with many eosinophils, some neutrophils and basophils, and eventually $CD4^+$ (T_{H2}) lymphocytes and macrophages.[3,9] These cells become activated and release more mediators, which in turn activate many of the proinflammatory reactions seen in the immediate response. Although eosinophils predominate in nasal secretions, $CD4^+$ (T_H) lymphocytes predominate in nasal biopsy specimens.[11]

Sleep disturbance from nasal congestion, and inflammatory cytokines released from inflammatory cells that circulate to the central nervous system, may elicit malaise, fatigue, irritability, and neurocognitive deficits that often accompany allergic rhinitis.[12]

Priming effect

The amount of allergen necessary to elicit an immediate response becomes less when allergen challenges are given repeatedly, a phenomenon called the priming effect.[1,3,13] It is thought that during ongoing, prolonged allergen exposure and repeated late phase/inflammatory responses that the nasal mucosa becomes progressively more inflamed and responsive to allergen. Clinically, this can explain why patients may have increasing symptoms despite decreasing aeroallergen levels as a season progresses. In addition, the priming effect from allergen is also associated with mucosal hyperresponsiveness to non-antigenic triggers such as strong odors and cigarette smoke.

Differential diagnosis

The classic symptoms of allergic rhinitis (rhinorrhea, nasal congestion, sneezing, nasal itching) frequently overlap with symptoms associated with other forms of rhinitis and various anatomic abnormalities of the upper airway. Post-nasal drainage occurs commonly, as may symptoms involving the ears, eyes, and throat. Nonallergic rhinitis without eosinophilia, sometimes termed idiopathic rhinitis, manifests as chronic nasal symptoms not caused by allergic or infectious processes. Symptoms are nasal obstruction and/or increased secretions, with sneezing and pruritus being less common. This clinical presentation is likely caused by a heterogenous group of disorders whose pathogenesis is incompletely understood. Vasomotor rhinitis refers to nasal symptoms that occur in response to environmental conditions, such as changes in temperature or relative humidity, odors such as perfume or cleaning materials, passive tobacco smoke, alcohol, sexual arousal, and emotional factors. Such hyperreactivity to non-allergic triggers may also occur in allergic rhinitis. There is no evidence that vasomotor rhinitis is caused by increased neural efferent traffic to the blood vessels supplying the nasal mucosa.[1,3] Accordingly, it has been suggested that the term "idiopathic rhinitis" should be used instead of vasomotor rhinitis.

Non-allergic rhinitis with eosinophilia syndrome (NARES) is characterized by perennial nasal symptoms (particularly nasal congestion), sneezing paroxysms, pro-

fuse watery rhinorrhea, nasal pruritus, and occasional loss of smell.[1,3] Nasal smears demonstrate eosinophils, but patients lack evidence of allergic disease by skin testing or by serum levels of IgE to environmental allergens. Patients are typically middle-aged. It has been proposed that the syndrome may be an early stage of aspirin sensitivity.[14]

Hormonal rhinitis may be caused by hormonal changes of pregnancy or puberty, the use of oral contraceptives or conjugated estrogens, or thyroid disorders. During pregnancy, congestion and other rhinitis symptoms frequently develop during the second month and persist to term, but usually resolve shortly after delivery. The pathogenesis likely involves hormone-induced intranasal vascular engorgement and mucosal hypersecretion. In women with preexisting rhinitis, symptoms may worsen, improve, or remain the same during pregnancy.[1,3,15]

Drug-induced rhinitis may be caused by either oral and topical medications. Causal oral medications include ACE inhibitors, beta blockers, various antihypertensive agents, chlorpromazine, aspirin, other non-steroidal anti-inflammatory drugs, and oral contraceptives. Use of topical alpha-adrenergic decongestant sprays for more than 5 to 7 days may induce rebound nasal congestion upon withdrawal.[1] Repeated use of intranasal cocaine and methamphetamines may also result in rebound congestion and on occasion, septal erosion and perforation.[1,16]

Rhinitis from food ingestion

Ingested food allergens rarely cause isolated rhinitis on an IgE-mediated basis without involvement of other organ systems.[1,17] Ethanol in beer, wine, and other alcoholic drinks may produce symptoms that have been proposed to occur because of pharmacologic nasal vasodilation.[1] Gustatory rhinitis is a cholinergically mediated syndrome of watery rhinorrhea occurring immediately after ingestion of foods, particularly hot and spicy foods.[18] It may occur as a distinct entity or accompany other types of rhinitis.

Atrophic rhinitis

Primary atrophic rhinitis occurs in elderly patients who report nasal congestion and a constant bad smell (ozena) in the nose.[1,19] However, most elderly patients with rhinitis symptoms have other more common types of rhinitis. Primary atrophic rhinitis is associated with progressive atrophy of the nasal mucosa and underlying bone and enlarged nasal cavities that become filled with foul smelling crusts. An infectious basis has been theorized.[20] Secondary atrophic rhinitis may develop from chronic granulomatous nasal infections, chronic sinusitis, radical nasal surgery, trauma, and irradiation.

Infectious rhinosinusitis

Acute viral upper respiratory infection presents with nasal symptoms and constitutional symptoms (fever, myalgias, malaise). Pruritus is typically absent and symptoms resolve within 7-10 days. Acute and chronic bacterial sinusitis may be difficult to distinguish from rhinitis on clinical grounds. (See discussion of sinusitis below).

Differential considerations other than rhinitis

Anatomic abnormalities usually present with prominent obstructive symptoms with less prominent symptoms of rhinorrhea.

Septal deviation may cause symptoms of unilateral or bilateral congestion, or recurrent sinusitis, although more often it is asymptomatic. Septal deviations can often be diagnosed by seeing the external deviation of the nose or by looking anteriorly with a nasal speculum. Diagnosis may require fiberoptic rhinopharyngoscopy or CT scanning.

Nasal polyps are benign, inflammatory growths that arise from the inflamed mucosa lining the paranasal sinuses. They may cause invariant unilateral or bilateral nasal obstruction and loss of smell or rhinorrhea. Polyps are infrequent in children, except for those with cystic fibrosis. Neutrophils are more characteristic of nasal polyps associated with cystic fibrosis.[21] Eosinophilic infiltrates are more typical of most polyps, including those associated with asthma and aspirin sensitivity,[3,22] which likely explains why corticosteroids are effective medical treatment. Nasal polyps are frequently associated with sinus disease. Unilateral nasal polyps should raise consideration of a possible neoplasm. The prevalence of nasal polyposis in allergic patients is typically under 5%.[3,23] Although it has been traditionally assumed that allergy is a cause of nasal polyps, the prevalence of documented allergy is not increased in patients with nasal polyps.[24] Aspirin sensitivity and asthma are associated with an increased risk for recurrent polyps that require repeat surgical polypectomies, but not allergy.[3,25]

Other differential considerations for nasal symptoms include nasal tumors that can be benign or malignant and can involve any element. Juvenile angiofibromas often present with bleeding in adolescent males. The most common presentation of tumors is obstruction. Nasal carcinoma may present with unilateral epistaxis and nasal pain. Young children may place intranasal foreign bodies in their noses (eg, small parts of toys) leading to foul smelling, purulent discharge and unilateral nasal obstruction that predisposes to sinusitis. Adenoidal hypertrophy in young children causes bilateral nasal obstruction and is often associated with nocturnal mouth-breathing and snoring. Wegener's granulomatosis may present with nasal and sinus complaints including purulent rhinorrhea and occasionally septal erosions and perforations. Sjogren's syndrome may cause nasal dryness, congestion, and crusting. Sarcoidosis may present with nasal congestion.

DIAGNOSIS

Full evaluation of a patient with rhinitis should include assessment of specific symptoms bothersome to the patient (eg, nasal congestion, pruritus, rhinorrhea, sneezing), the pattern of symptoms (eg, intermittent, seasonal, perennial), identification of precipitating factors, response to medications, coexisting conditions, and a detailed environmental history including home and occupational exposures.[1] Nasal itching is more suggestive of allergic rhini-

tis. Because allergic rhinitis is frequently associated with allergic conjunctivitis, the presence of eye pruritus and lacrimation is a helpful indication that a patient's rhinitis has an allergic basis. In most regions of the US, trees pollinate in the spring, grasses in the late spring and early summer, and weeds in the late summer and fall. However, in some regions (eg, portions of California) pollens may cause perennial symptoms. Perennial allergens such as house dust mites, cockroaches, and animals cause symptoms that vary little between seasons, making it difficult to accurately distinguish between allergic and nonallergic rhinitis on the basis of history alone. Family history is an important clue in making the diagnosis of allergic rhinitis in children. A hand-held otoscope or headlamp with nasal speculum permits viewing of the anterior one-third of the nasal airway including the anterior tip of the inferior turbinates (and occasionally the anterior tip of the middle turbinates) and portions of the nasal septum. Treatment with a topical decongestant improves visualization of the nasal cavity. However, some nasal polyps, septal deviation, and masses may be missed beeause of the inability to visualize the posterior and superior nasal airway. Typically, patients with allergic rhinitis have clear discharge, swollen turbinates, and bluish or pale mucosa. Pale or erythematous mucosa can be seen in various types of non-allergic rhinitis. Both allergic and non-allergic rhinitis can cause "allergic shiners," infraorbital darkening thought due to chronic venous pooling, or an "allergic salute" in children who rub their noses upward because of nasal discomfort, sometimes producing a persistent horizontal crease across the nose.

In association with rhinitis, physical findings of bilateral conjunctivitis (mild injection with non-purulent discharge) are suggestive of allergy. Patients with nasal disease require appropriate examination for associated diseases, such as sinusitis and otitis media.

Diagnostic testing

Determination of specific IgE antibodies to known allergens by skin testing or in vitro tests is important for identifying specific allergens when avoidance measures or allergen immunotherapy are being contemplated.[1] In perennial rhinitis, history is usually insufficient for distinguishing allergie from non-allergic rhinitis, and testing is of added importance. Neither total serum IgE nor total circulating eosinophil counts are routinely indicated in the diagnosis of rhinitis as they are neither sensitive nor specific for allergic rhinitis.[1]

Nasal cytology may aid in differentiating allergic rhinitis and NARES from other forms of rhinitis, such as vasomotor or infectious rhinitis, if the correct procedure is followed and the appropriate stains are utilized. However, there is lack of expert consensus about whether nasal cytology should be routinely used in the diagnosis of rhinitis.[1]

In selected cases, special techniques such as fiberoptic nasal endoscopy, inspiratory peak flow measurements, acoustic rhinometry, or rhinomanometry to assess airway function may be useful in evaluating patients presenting with rhinitis symptoms.

TREATMENT

Avoidance measures

Avoidance of inciting factors, such as allergens (house dust mites, molds, pets, pollens, cockroaches), irritants, and medications, can effectively reduce symptoms of rhinitis. In particular, patients allergic to house dust mites should use allergen-impermeable encasings on the bed and all pillows. Pollen exposure can be reduced by keeping windows closed, using an air conditioner, and limiting the amount of time spent outdoors.

Medications

Medications should be selected in consideration of the individual patient's symptoms and type of rhinitis, because different medications may have different effects on different types of rhinitis and symptoms. In more severe rhinitis, several medications may be required. A step-wise approach to management is recommended, emphasizing individualization of treatment, on the basis of the spectrum and severity of symptoms, with consideration of cost effectiveness and utilization of both step-up and step-down approaches.[1] Failure to adequately respond to therapy should prompt referral to an allergy/immunology or otolaryngologic allergy specialist.

Oral antihistamines

Antihistamines reduce sneezing, rhinorrhea, and nasal and ocular pruritus associated with allergic rhinitis, but have less effect on nasal congestion.[1,3] Antihistamines are effective when taken occasionally for episodic symptoms, but they work best when administered on a regular basis. Antihistamines are a first line therapy for milder allergic rhinitis,[1] but have little role in treating non-allergic rhinitis syndromes. Antihistamines reduce symptoms of allergic conjunctivitis, which are often associated with allergic rhinitis, although intranasal corticosteroids are equally effective.

Older, first-generation antihistamines (eg, diphenhydramine and chlorpheniramine) may cause perceived sedation and unperceived impairment of mental functioning that can be potentiated by other central nervous system active agents (eg, alcohol, sedatives, anti-depressants).[26] They have been implicated as causal faetors in fatal automobile accidents, decrease work performance and produetivity, and impair children's learning and academic performance.[1,27-29] The first-generation antihistamines also may cause anti-cholinergic side effects such as dry month, blurred vision, and urinary retention. Second-generation antihistamines that are associated with less risk (cetirizine) or no risk for these side effects compared to placebo (desloratadine, loratadine, fexofenadine) should usually be considered before sedating antihistamines for treatment of allergic rhinitis.[1]

Oral decongestants (eg, pseudoephedrine, phenylephrine) can effectively reduce nasal congestion produced by allergic and non-allergic forms of rhinitis.[1,30] They can cause insomnia, nervousness, loss of appetite, and urinary retention in males, and should be used with

caution in patients with certain conditions, eg, arrhythmias, hypertension, and hyperthyroidism.

Topical decongestant nasal sprays (eg, oxymetazoline, phenylephrine) may reduce nasal congestion in both allergic and non-allergic rhinitis, but should be limited to 3-5 days' use to avoid rebound nasal congestion (rhinitis medicamentosa). In more severe rhinitis with nasal edema that prevents delivery of other types of nasal sprays (eg, nasal corticosteroids) to more superior regions of the nose, use of nasal decongestant sprays during the first few days of administration of other sprays is used to improve treatment outcomes. Systemic side effects are not usually observed with these intranasal agents, although topical decongestants in infants have been reported to cause seizures.

Intranasal corticosteroids are the most effective medication class for treatment of allergic rhinitis, and are particularly useful for more severe allergic rhinitis.[1] In addition, this class is useful in some forms of non-allergic rhinitis. Currently used preparations are generally not associated with significant systemic side effects in adults.[31] Linear growth suppression in young children has been reported with intranasal beclomethasone taken for 1 year,[32] but not from several other nasal corticosteroid preparations.[33-35] Patients should be instructed to direct sprays away from the nasal septum. Although local side effects are minimal if the patient is carefully instructed about use, nasal irritation and bleeding may occur. The nasal septum should be periodically examined to assure that there are no mucosal erosions that may precede development of nasal septal perforations that are rarely associated with intranasal corticosteroids.[1] Although these drugs are most beneficial when dosed on a regular schedule, studies with some agents have demonstrated an onset of effect within several hours, and fluticasone nasal has been demonstrated to be beneficial for allergic rhinitis when used on an as-needed basis.[36]

Intranasal azelastine is an antihistamine effective for treatment of allergic rhinitis and vasomotor rhinitis.[37,38] This agent is appropriate for use as first-line treatment for allergic rhinitis.[1] It is at least as effective for allergic rhinitis as oral antihistamines but less effective than nasal corticosteroids.[39] It is effective on nasal obstruction, but less so than intranasal glucocorticosteroids.[40] Side effects may include a bitter taste and sedation.

Intranasal cromolyn sodium is effective for symptoms of allergic but not non-allergic rhinitis. It is usually less effective than oral antihistamines, intranasal antihistamines or corticosteroids.[3,41] Optimally administered 4 to 6 times daily, cromolyn should ideally be started before major symptoms develop as it may take several weeks to be effective if a patient has been experiencing significant symptoms. It can also be used for acute prophylaxis before exposure to a known allergen. Cromolyn has an excellent safety profile.

Intranasal ipratropium bromide is an anti-cholinergic agent effective for reducing watery nasal secretions in allergic rhinitis, non-allergic rhinitis, and viral upper respiratory infections.[1-3] It has no significant effect on other nasal symptoms however. Ipratropium does not cause significant systemic anticholinergic effects. If a patient's rhinorrhea is acutely triggered by known stimuli (eg, spicy food), ipratropium may be given prophylactically at least 15 minutes before exposure.

Systemic corticosteroids. Short-acting oral corticosteroids (eg, prednisone, methylprednisolone) are used in brief courses (eg, prednisone 30 mg/QD for 3-7 days for adults) for the treatment of very severe or intractable nasal symptoms. Use of parenteral corticosteroids is discouraged because of greater potential for HPA axis suppression and long-term corticosteroid side effects.[1]

Leukotriene receptor antagonists. These agents have been demonstrated to have benefit in seasonal allergic rhinitis, but data are inadequate to define their role in therapy.[3,42]

Anti-IgE therapy. The monoclonal antibody Omalizumab has been shown to have some benefit in allergic rhinitis,[43] but further studies are needed to compare its effect with other available therapies. There is no expectation that the long-term course of allergic rhinitis is modified by anti-IgE, unlike conventional specific allergen immunotherapy.

Allergen immunotherapy/allergy vaccination

Allergen immunotherapy may be highly effective in controlling symptoms of allergic rhinitis, and is the only method demonstrated to favorably modify the long-term course of the disease.[44] Patients with allergic rhinitis should be considered candidates for immunotherapy on the basis of the severity of their symptoms, failure or unacceptability of other treatment modalities, presence of co-morbid conditions, and possibly as a means of preventing worsening of the condition or the development of co-morbid conditions (eg, asthma, sinusitis).[1] Approximately 80% of patients will experience symptomatic improvement after 1-2 years, and guidelines recommend that treatment be continued for a total of 4-5 years. In many patients, the beneficial effects persist for years after injections are stopped.

Considerations in select populations

Children. Because some nasal corticosteroid preparations have been reported to reduce linear growth (at least temporarily), growth should be monitored in children receiving these agents.

Elderly. Allergy is an uncommon cause of perennial rhinitis in individuals over 65 years of age. More commonly, rhinitis in the elderly is due to cholinergic hyperreactivity (associated with profuse watery rhinorrhea which may be aggravated after eating, "gustatory rhinitis"), alpha adrenergic hyperactivity (congestion associated with antihypertensive drug therapy), or sinusitis.[1] Because the elderly may have increased susceptibility to the adverse CNS and anticholinergic effects of antihistamines, non-sedating agents are recommended if antihistamines are used for allergic rhinitis. Oral decongestants should be used with caution in this patient subset because of their effects on the CNS, heart, and bladder function.

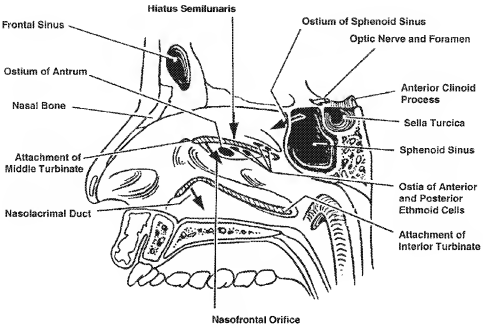

FIG 1. Lateral nasal wall with the location of sinuses and their orifices in particular the anterior ethmoid. (From Montgomery WW. Surgery of the Upper Respiratory System. Philadelphia, Lea and Febiger, 1979. With permission of Lippincott Williams and Wilkins.)

Pregnancy. Nasal cromolyn has the most reassuring safety profile in pregnancy. Cetirizine, chlorpheniramine, loratadine, and tripelennamine have been rated FDA pregnancy category B, a more favorable rating than category C rating of other antihistamines. Intranasal budesonide has a category B rating; other nasal corticosteroids are rated category C, although beclomethasone dipropionate has the longest experience in use in pregnancy. Oral decongestants are best avoided in the first trimester because of the risk of gastroschisis in the newborn.[45] Allergen immunotherapy should not be started or advanced in dose during pregnancy, but may be continued at a stable dose.

SINUSITIS

Background

Sinusitis is defined as inflammation of 1 or more of the paranasal sinuses, air-filled cavities in facial bones lined with pseudostratified ciliated columnar epithelium and mucous goblet cells. Acute bacterial sinusitis is defined to be less than 4 weeks' duration. Subacute sinusitis is frequently defined to be of 4 to 12 weeks' duration. Chronic sinusitis, defined to be symptoms lasting longer than 12 weeks (with some guidelines also requiring a failure to respond to treatment and a positive imaging study), can be caused by bacterial infection, but other processes frequently are operative in sustaining chronic sinusitis. Chronic sinusitis is 1 of the most common chronic medical conditions in the US. Recurrent sinusitis refers to repeated episodes of acute sinusitis, typically ≥3 times per year. Recurrent acute sinusitis is often defined as ≥4 episodes per year, with each episode lasting ≥7-10 days, and absence of intervening signs and symptoms of chronic rhinosinusitis.

PATHOGENESIS

Anatomy and physiology

Epithelial cilia in the sinuses normally beat mucus towards the ostia that communicate with the nasal cavity. The anterior ethmoid, maxillary, and frontal sinuses drain into the ostiomeatal complex, located in the middle meatus (Fig 1). The sphenoid sinuses drain into the posterior wall in the spheno-ethmoidal recess, and the posterior ethmoids drain into the upper meatus. Normal paranasal sinuses have relatively few glands, whereas inflamed sinus mucosa contains newly developed and pathological mucous glands.[3,46] Viscoelastic mucus contributes to post-nasal drip.

Etiology and predisposing factors

The development of acute sinusitis is promoted by several factors: obstruction of the sinus ostia, impaired ciliary function, viscous secretions, and impaired host immunity (eg, selective IgA deficiency).[2] Mucosal edema, as may occur from rhinitis or anatomic abnormalities (eg, nasal polyps, pronounced septal deviation) that obstruct drainage from or ventilation of sinuses, promotes mucus accumulation, serum transudation, and decreased oxygenation within the sinuses. These changes result in impaired ciliary movement of mucus and pro-

motion of bacterial growth. The term rhinosinusitis is increasingly used in recognition that rhinitis (whether allergic or non-allergic) typically precedes sinusitis. Sinusitis without rhinitis is rare, the mucosa of the nose and sinuses are contiguous, and symptoms of nasal obstruction and nasal discharge are prominent in sinusitis. If acute sinusitis does not resolve, persistent anatomic and functional changes in the sinuses occur that promote development of chronic sinusitis.

In chronic sinusitis, there is development of mucosal hyperplasia, usually accompanied by eosinophilic tissue infiltrates. Nasal polyps may also develop. Current evidence indicates that TH_2 lymphocytes play an important role in sustaining this pathology. The common association between rhinosinusitis and asthma suggests that a common pathogenesis promotes eosinophilic infiltrates in the upper and lower airway.[2]

Microbiology of acute, chronic, and recurrent sinusitis

Most cases of infectious rhinosinusitis of less than 7 days' duration are viral.[2,47,48] Organisms commonly causing acute bacterial sinusitis are *Streptococcus pneumoniae* and *Hemophilus influenzae*, and primarily in children, *Moraxella catarrhalis*.[49] When chronic sinusitis involves ongoing infection, these organisms and others may be involved including: *Pseudomonas aeruginosa*, group A *Streptococcus*, and *Staphylococcus aureus*. Although anaerobes such as *Bacteroides* species, *Fusobacteria* and *P acnes* had been considered important, most recent data question this. Fungal infections are recognized as causes of chronic sinusitis, but most evidence indicates that bacterial infections are the most common infectious causes of chronic sinusitis. Fungal infections are more likely to occur in diabetes mellitus and immunocompromised patients and in geographic areas with high humidity. Fungal sinus infections may be non-invasive, invasive, or result in a fungal ball. A distinct entity, allergic fungal sinusitis, occurs in non-immunocompromised patients and results from a hypersensitivity response to fungi such as Aspergillus that colonize the sinuses.[50]

DIAGNOSIS

Presentation of sinusitis is highly variable, and it is sometimes difficult to distinguish from rhinitis without sinusitis. No single symptom or sign is diagnostic. Nonetheless, the overall presentation of history and physical findings is usually sufficient to make the diagnosis of acute, uncomplicated sinusitis. Diagnostic testing becomes important when initial therapy fails, or when symptoms are chronic or recurrent.

History

Acute bacterial sinusitis in adults most often presents with ≥7 days of symptoms of purulent anterior rhinorrhea, nasal congestion, postnasal drip, facial or dental pain/pressure, and cough, frequently with a nighttime component.[2,47] Children with acute sinusitis most commonly have cough and rhinorrhea.[2,48] In all age groups with acute sinusitis, less frequent symptoms may include fever, nausea, fatigue, anosmia, and halitosis.

Chronic rhinosinusitis may cause symptoms that persist for months to years, and may be less severe than those of acute rhinosinusitis. Nasal obstruction or posterior discharge are usually chief complaints of chronic rhinosinusitis. Chronic cough (especially during the night or upon awakening in the morning) is also a common presenting symptom of chronic rhinosinusitis. Clinical evidence of sinusitis occasionally may be subtle, except during acute purulent episodes.

Physical findings

Typical physical signs include nasal mucosal edema, sinus tenderness (although this is neither a sensitive nor a specific finding), and purulent nasal secretions. The presence of purulent secretions has the highest positive predictive value of all physical signs.

The nose should be examined for deviated septum, nasal polyps, foreign bodies, and tumors. Maxillary sinusitis is suggested by sensitivity of the maxillary teeth. The ears and chest should be examined for signs of associated otitis media and asthma.[2]

Findings that suggest need for immediate referral

Facial swelling over an involved sinus, proptosis, abnormal extraocular movements, visual changes, periorbital edema, and CNS symptoms (eg, changes in mental status) may indicate intracranial complications of acute sinusitis (eg, periorbital abscess, brain abscess, or meningitis), and should prompt referral for immediate surgical consultation.[2] Severe headaches and high fevers are other presentations that may require immediate referral.

Imaging studies

Radiologic studies performed within days of the onset of acute rhinosinusitis symptoms may lead to an incorrect conclusion that bacterial infection is present. Up to 40% of sinus radiographs and more than 80% of CT scans may be abnormal in viral rhinosinusitis if obtained within 7 days of the onset of illness.[51] In routine cases of suspected acute bacterial rhinosinusitis, imaging studies are not required.[2,47,48] When there are more persistent symptoms as in chronic sinusitis or an incomplete response to initial management, imaging studies become appropriate. Radiographic signs consistent with acute sinusitis include opacification/air fluid levels in any paranasal sinus, >6 mm mucosal thickening in the maxillary sinuses, and >33% loss of air space volume within the maxillary sinuses.[2] Although Caldwell (anterior-posterior) radiographs are useful for identifying frontal sinusitis, and Waters view radiographs are of moderate sensitivity for identifying maxillary sinusitis, they are less useful for identifying pathology of other sinuses, and have little value for identifying ethmoid sinusitis, of key importance in many cases of chronic sinusitis.

Sinus CT scans identify disease not demonstrated by standard radiographs, and are of particular value in assessing obstruction of the sinus ostia. CT scans are appropriate when medical therapy has failed, and to establish the diagnosis in equivocal cases of chronic sinusitis before starting long-term antibiotic therapy. In some localities, a limited 4- or 5-image sinus CT scan with coronal views can be performed at a cost only marginally higher than standard radiographs. A complete series sinus CT scan fully defines sinus anatomy and is a prerequisite for sinus surgery. Suspected orbital involvement is best identified by axial views.

When fungal sinusitis and tumors are suspected, magnetic resonance imaging (MRI) is preferred. MRI does not distinguish air from bone. Because examination of the air-bone interface is important in the evaluation of anatomic defects, MRI is not used for routine evaluation of suspected sinusitis.

Other diagnostic testing

The identification of large numbers of neutrophils in nasal secretions by nasal cytology can help distinguish between infectious sinusitis and rhinitis.[2] Transillumination is not reliable in diagnosing sinusitis.

Differential considerations

Distinguishing rhinitis from sinusitis is the most common clinical dilemma, although other disorders associated or predisposing to sinusitis (Table I) are differential considerations. Migraine headaches and fibromyalgia are relatively common conditions that should be considered in the differential diagnosis of chronic sinusitis. When patients present with recurrent or chronic infections of both the upper and lower respiratory tracts, an immunodeficiency should be considered.

TREATMENT

Initial treatment of sinusitis

When symptoms suggestive of rhinosinusitis persist beyond approximately 7 days, bacterial rhinosinusitis becomes more likely. Antibiotic usage is appropriate when moderate to severe symptoms are present, although most cases of milder acute bacterial rhinosinusitis will resolve without the need to prescribe antibiotics. In a study comparing antimicrobial therapy with placebo in the treatment of children with the clinical and radiographic diagnosis of acute bacterial sinusitis, those receiving antimicrobial therapy recovered more quickly and more often than those receiving placebo.[52] On the third day of treatment, 83% of children receiving an antimicrobial were cured or improved compared with 51% of children in the placebo group. On the 10th day of treatment, 79% of children receiving an antimicrobial were cured or improved compared with 60% of children receiving placebo.

Antibiotics

When antibiotics are used for acute sinusitis, a 10- to 14-day treatment course is typically prescribed. Antibiotic choice should consider cost, safety and local patterns of bacterial resistance to antibiotics.

TABLE I. Conditions associated with or predisposing to sinusitis

Rhinitis (allergic and non-allergic)
Viral URI
Asthma
Physical or chemical trauma, barotrauma
Anatomic obstruction: nasal polyps, septal deviation, adenoidal hyperplasia, concha bullosa (aerated middle turbinate), foreign body
Cleft palate
Dental infection
Systemic diseases (rare): antibody deficiency, ciliary dyskinesis, cystic fibrosis, Wegener's granulomatosis

In many geographic areas, amoxicillin is a reasonable first-line antibiotic. Although trimethoprim-sulfamethoxazole and (in children) erythromycin-sulfisoxazole have traditionally been used as first line antibiotics for patients with acute bacterial sinusitis, surveillance studies indicate development of significant pneumococcal resistance from alteration of penicillin binding proteins.[53,54] In addition, currently approximately 50% of *H influenzae* and 100% of *M catarrhalis* are likely to be β-lactamase positive nationwide.[55,56] In some areas beta-lactamase resistance is being found in up to 20% to 30% of bacterial isolates. Erythromycin alone provides unsatisfactory coverage for sinusitis, although the macrolides clarithromycin and azithromycin have expanded coverage and are effective against β-lactamase producing organisms. When first-line agents have failed or there is a high prevalence of β-lactamase resistance, amoxicillin/clavulanate or second or third-generation cephalosporins (eg, cefuroxime, cefpodoxime, cefprozil) provide broader coverage. These agents are available as suspensions that can be easily used in young children. A guideline of the American Academy of Pediatrics[48] recommends that for sinusitis that is moderate or more severe, if a child has recently received another antibiotic or attends day care, therapy should be initiated with high-dose amoxicillin-clavulanate (80-90 mg/kg/d of amoxicillin component, with 6.4 mg/kg/d of clavulanate in 2 divided doses).

First-generation cephalosporins (eg, cephalexin) have poor *H influenzae* coverage, and while second-generation cephalosporins (eg, cefaclor) provide improved coverage, resistance by *H influenzae* and *M catarrhalis* is becoming common.

In adults, several quinolones (eg, ciprofloxacin, gatifloxacin, levofloxacin, moxifloxacin) have specific indications for the treatment of sinusitis, but these should be reserved for second or third-line use or for more serious infections.[2]

Expert consensus is that chronic sinusitis should be treated with antibiotics for 3 weeks or longer, although there is a relative paucity of controlled trials.[2]

Other medications

Comprehensive treatment of bacterial sinusitis may require use of antibiotics, analgesics, adequate hydration, steam inhalation, and pharmacologic measures intended to treat underlying disease such as rhinitis and to restore ostial patency. Short term (3-5 days) use of topical nasal decongestants and oral decongestants are used in acute or chronic sinusitis to reduce turbinate swelling and mucosal edema that can compromise ostial patency. Although there are little data from controlled trials, second-generation H_1 antihistamines are logical additions to therapy when concomitant allergic rhinitis is present. Avoidance of first-generation antihistamines has been advised because of the theoretical potential of these drugs for causing anti-cholinergic drying effects and impairment of mucus clearance, but there are no controlled trials that have demonstrated less favorable clinical outcomes from their use. Nasal glucocorticosteroids are thought to be potentially effective adjuncts to antibiotic therapy, but available objective data have not unequivoeally demonstrated effectiveness.[57-60] The short-term use of oral corticosteroids as an adjunct in treating acute sinusitis is considered reasonable when the patient has nasal polyps or severe mucosal edema, although efficacy is not yet proven in controlled trials. Saline spray or irrigation is recommended to fiquefy secretions. Although there are no controlled trials demonstrating efficacy, high-dose guaifenesin (1200 mg BID) is used empirically in an effort to thin tenacious respiratory secretions and promote mucus drainage from the sinuses.

When initial therapy fails

If acute sinusitis does not improve after several days of antibiotics, prescription of an alternative antibiotic for several additional weeks should be considered.[2] If there is still no response, a sinus CT is indicated to confirm the presence of sinusitis and determine if anatomic abnormalities may be predisposing to sinusitis. Specialist evaluation is appropriate when sinusitis is refractory to treatment or is recurrent. Because chronic sinusitis is associated with allergic rhinitis in 40%-80% of adults and 36%-60% of children, patients with chronic sinusitis should be evaluated for allergy so that environmental control measures or other interventions appropriate for allergic (but not non-allergic) disease can be implemented.[2] A specialist's evaluation can also assess whether there is another immunologic basis for sinusitis and address conditions that may be complicating assessment or management, such as asthma, nasal polyps, allergic fungal sinusitis, chronic otitis media, immunodeficiency, and multiple antibiotic sensitivities. In patients with aspirin sensitivity and hyperplastic sinus disease, aspirin desensitization has been demonstrated to improve long-term outcome. Fiberoptic rhinoscopy can reveal the presence or extent of nasal polyps, septal deviation, or mucopurulent secretions. In refractory sinusitis, referral to an otolaryngologist for sinus culture by aspiration can help direct choice of antibiotics. In children, there are no data that have correlated cultures of the middle meatus with cultures of the maxillary sinus aspirate.[61] Surgical intervention should be considered if sinusitis does not respond to medical intervention. Functional endoscopic sinus surgery (FESS) has generally supplanted older surgical techniques.[62] FESS is typically directed at removal of locally diseased ethmoid tissue (important in the development of frontal and maxillary sinusitis) to improve ventilation and drainage of larger, dependent sinuses.

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